AMENDMENTS

In the Claims:

1. (Withdrawn) A method to detect a nucleotide, nucleoside, or base, comprising:

a) depositing the nucleotide, nucleoside, or base on a substrate comprising aluminum or comprising a metal-coated nanostructure;

b) irradiating the deposited nucleotide, nucleoside, or base; and

c) detecting Raman spectra from the irradiated nucleotide, nucleoside, or base, thereby detecting the nucleotide, nucleoside, or base.

2. (Withdrawn) The method of claim 1, wherein the nucleotide, nucleoside, or base is deposited on one or more silver nanoparticles between about 5 and 200 nm in diameter, before being detected.

3. (Withdrawn) The method of claim 2, wherein the nucleotide, nucleoside, or base is contacted with an alkali-metal halide salt before being detected.

4. (Withdrawn) The method of claim 3, wherein the alkali-metal halide salt is lithium chloride.

5. (Withdrawn) The method of claim 4, wherein the nucleotide, nucleoside, or base comprises adenine.

6. (Withdrawn) The method of claim 5, wherein the lithium chloride is used at a concentration of about 50 to about 150 micromolar.

7. (Withdrawn) The method of claim 5, wherein the lithium chloride is used at a concentration of about 90 micromolar.

8. (Withdrawn) The method of claim 7, wherein 10 or less molecules of a nucleotide, nucleoside, or base comprising adenine are detected.

9. (Withdrawn) The method of claim 7, wherein 1 molecule of a nucleotide, nucleoside, or base comprising adenine is detected.

10. (Withdrawn) The method of claim 4, wherein the nucleotide, nucleoside, or base comprises guanine.

11. (Withdrawn) The method of claim 10, wherein between about 50 and about 100 molecules of a guanine base are detected.

12. (Withdrawn) The method of claim 4, wherein the nucleotide, nucleoside, or base comprises cytosine.

13. (Withdrawn) The method of claim 12, wherein between about 1000 and 10000 molecules of a cytosine base are detected.

14. (Withdrawn) The method of claim 4, wherein the nucleotide, nucleoside, or base comprises thymine.

15. (Withdrawn) The method of claim 14, wherein between about 1000 and 10000 molecules of a thymine base are detected.

16. (Withdrawn) The method of claim 1, wherein the nucleotide, nucleoside, or base are associated with a Raman label.

17. (Withdrawn) The method of claim 1,wherein a base is detected.

18. (Currently amended) An apparatus comprising:

a) a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface;

b) an inlet channel in fluid communication with the reaction chamber;

c) an outlet channel in fluid communication with the reaction chamber;

d) a first Raman detection unit operably coupled to the inlet channel and configured to perform surface enhanced Raman spectroscopy (SERS); and

e) a second Raman detection unit operably coupled to the outlet channel and configured to perform surface enhanced Raman spectroscopy (SERS).

19. (Previously presented) The apparatus of claim 18, wherein each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level.

20. (Previously presented) The apparatus of claim 18, wherein the concentrations of nucleotides is measured by Raman spectroscopy as they flow through the inlet channel and outlet channel.

21. (Currently amended) The apparatus of claim 18, further comprising SERS active metal nanoparticles in the inlet channel and outlet channel.

22. (Previously presented) The apparatus of claim 18, wherein the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter.

23. (Currently amended) The apparatus of claim 18, further comprising a mesh inside the inlet channel or the outlet channel comprising ~~made of~~ silver, gold, platinum, copper or aluminum SERS active metal nanoparticles.

24. (Withdrawn) A method to determine a nucleotide occurrence at a target position of one or more template nucleic acid molecules, comprising:

a) contacting the one or more template nucleic acid molecules with a reaction mixture comprising a primer, a polymerase, and an initial concentration of a first nucleotide, wherein the 3' nucleotide of the primer binds to the template nucleic acid adjacent to the target nucleotide position to form a post-reaction mixture; and

b) determining the concentration of the first nucleotide in the post-reaction mixture using Raman spectroscopy, wherein a decrease in the post-reaction concentration of the first nucleotide identifies an extension reaction product, thereby identifying the nucleotide occurrence at the target position; and

c) repeating steps a-b with a different nucleotide until the nucleotide occurrence is identified.

25. (Withdrawn) The method of claim 24, wherein the nucleotide is attached to a Raman label before it is detected by Raman spectroscopy.

26. (Withdrawn) The method of claim 24, wherein the nucleotide is attached to a fluorophore before it is detected by Raman spectroscopy.

27. (Withdrawn) The method of claim 24, wherein the one or more template nucleic acid molecules are isolated from a biological sample before being contacted with the first reaction mixture.

28. (Withdrawn) The method of claim 24, wherein the concentration of a purine base is detected.

29. (Withdrawn) A method to sequence one or more nucleic acid molecules, comprising:

a) contacting the one or more template nucleic acid molecules with nucleotides, a primer, and a polymerase to form a reaction mixture, the one or more template nucleic acid molecules or the primer being immobilized on a solid support;

b) synthesizing one or more complementary strands to the one or more template nucleic acid molecules;

d) measuring the concentrations of the nucleotides in the reaction mixture by Raman spectroscopy; and

e) determining the sequence of the template nucleic acid from the nucleotides incorporated into the complementary strand.

30. (Withdrawn) The method of claim 29, further comprising separating the nucleotides from the template nucleic acid molecule before the nucleotide concentrations are measured.

31. (Withdrawn) The method of claim 29, wherein a single type of nucleotide is exposed to the template at one time.

32. (Withdrawn) The method of claim 29, wherein all four types of nucleotides are exposed to the template simultaneously.

33. (Withdrawn) The method of claim 29, wherein Raman labels are attached to each nucleotide.

34. (Withdrawn) The method of claim 29, wherein Raman labels are attached to the pyrimidine nucleotides.

35. (Withdrawn) The method of claim 29, wherein the nucleotide concentrations are measured by surface enhanced Raman scattering, surface enhanced resonance Raman scattering, stimulated Raman scattering, inverse Raman, stimulated gain Raman spectroscopy, hyper-Raman scattering or coherent anti-Stokes Raman scattering.

36. (New) An apparatus comprising:

a) a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface;

b) an inlet channel in fluid communication with the reaction chamber;

c) an outlet channel in fluid communication with the reaction chamber;

d) a first Raman detection unit operably coupled to the inlet channel, wherein surface enhanced Raman spectroscopy (SERS) active particles are in the inlet channel; and

e) a second Raman detection unit operably coupled to the outlet channel, wherein SERS active particles are in the outlet channel.

37. (New) The apparatus of claim 36, wherein each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level.

38. (New) The apparatus of claim 36, wherein the concentrations of nucleotides is measured by Raman spectroscopy as they flow through the inlet channel and outlet channel.

39. (New) The apparatus of claim 36, wherein the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter.

40. (New) The apparatus of claim 36, further comprising a mesh inside the inlet channel or the outlet channel comprising silver, gold, platinum, copper or aluminum SERS active metal nanoparticles.